especially with a falling partial oxygen pressure or pH, decreasing urine output or early signs of a coagulopathy—should rapidly receive a 30 mg per kg infusion of MPSS (over 10 to 20 minutes) followed by a constant MPSS infusion of 5 mg per kg per hour for eight to ten hours. The constant infusion should be discontinued when the patient becomes well stabilized. Even if shock develops or persists, the MPSS infusion should probably not be continued beyond the initial eight- to ten-hour period. The incidence of secondary suprainfections increases the longer high doses of a glucocorticoid are administered. The constant MPSS infusion method is preferred over intermittent "bolus-type" infusions based on well-done studies on animals by Hinshaw's group in Oklahoma City[4,5]; for whatever reason, constant infusion of MPSS produces significantly better results both in dogs and baboons than do intermittent boluses.

An infusion of antiendotoxin antiserum will also help patients survive Gram-negative bacteremia. Endotoxinlike moieties also exist in the cell walls of Gram-positive bacteria (the peptidoglycan-teichoic acid complex) and in yeast (zymosan-like substances), and those substances trigger the same series of metabolic events under proper circumstances as does endotoxin from the cell wall of Gram-negative bacteria. Thus, though not yet studied, antisera could theoretically be developed and would probably prove to be useful in patients with Gram-positive bacteremia or fungemia. As Jacobson and Young point out, the commercial development of human monoclonal antiendotoxin antibodies is under way and "may become an important part of the therapy undertaken for Gram-negative bacteremia in the near future." I agree! Studies are needed assessing whether antiserum therapy will obviate the need for steroids or whether steroid therapy in any way impairs the effect of antiendotoxin antibody administration.

The authors review the massive activation of the endorphin system in sepsis and the rationale, therefore, for the use of naloxone to counter endorphin-induced hypotension. While the rationale for the use of naloxone is clear, the true clinical effectiveness of the agent is not! As stated by the authors, no evidence exists that prolongation of survival in primates or humans is achievable by the use of naloxone. My own feeling is that volume, antibiotics and, in appropriate subgroups of patients with severe sepsis, glucocorticoids are the mainstays of treatment of bacteremia. Naloxone may help stabilize some patients who continue in shock, requiring increasing doses of vasoactive and cardioactive pharmacologic agents. Occasionally such a patient can be weaned off high doses of dopamine through the use of constant infusions of high doses of naloxone, as outlined by Jacobson and Young.

Finally, and more philosophically, I believe we need to better define subgroups of patients that should *not* be aggressively treated for septicemia. Patients critically ill with rapidly or ultimately fatal diseases who are highly likely to have bacteremia as an expected complication not only do not do well even with aggressive therapy but experience prolonged, uncomfortable and expensive treatment in our intensive care units before death inevitably supervenes. Intensive care unit support *can* extend life in such patients, as shown clearly by Sprung and co-workers[6]; long-term survival, however, is usually not improved. It is useful to remember that untreated sepsis, though unpleasant to observe, is probably a comfortable terminal event because of massive endorphin release. Understanding the role of endogenous endorphin release in severe sepsis explains why "pneumonia is the old man's friend." I would suggest that sepsis also befriends the incurably ill.

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REFERENCES

1. Sheagren JN: Shock syndromes related to sepsis, *In* Wyngaarden JB, Smith LH Jr (Eds): Cecil Textbook of Medicine, 17th Ed. Philadelphia, Saunders, 1985, pp 1473-1477

2. Demling RH: Colloid or crystalloid resuscitation in sepsis, *In* Sibbald WJ, Sprung CL (Eds): New Horizons Perspectives on Sepsis and Septic Shock. Fullerton, Calif, SCCM, 1985, pp 275-300

3. Sheagren JN: Glucocorticoid therapy in the management of severe sepsis, *In* Sande M, Root R (Eds): Septic Shock. New York, Churchill-Livingstone, 1985, pp 201-218

4. Hinshaw LB, Beller-Todd BK, Archer LT, et al: Effectiveness of steroid/antibiotic treatment in primates administered LD_{100} *Escherichia coli*. Ann Surg 1981; 194:51-56

5. Beller BK, Archer LT, Passey RB, et al: Effectiveness of modified steroid-antibiotic therapies for lethal sepsis in the dog. Arch Surg 1983; 118:1293-1299

6. Sprung CL, Caralis PV, Marcial EH, et al: The effects of high-dose corticosteroids in patients with septic shock: A prospective controlled study. N Engl J Med 1984; 311:1137-1143

'Society Must Decide'

AN ARTICLE BY RALPH CRAWSHAW appearing elsewhere in this issue introduces two new concepts into the difficult problem of deciding on health service priorities relative to all other social, economic and political priorities when there are not enough resources to do everything for everyone. The first is a concept of biovalues which Crawshaw separates from the concept of bioethics. Biovalues are the values a community or society places on health and life as measured in dedicated social resources such as tax dollars. Bioethics, in this context at least, pertains to what is good and bad health care practice and to moral obligations and duties of physicians, families and others toward patients, rather than to how society allocates its resources.

A second concept is the process through which biovalues were developed in the Oregon Health Decisions project that is described in this article. What appears to be a new concept is the development of what was found to be a workable community-based method of addressing such questions as, how can the present implicit rationing of health care be made explicit and part of recognized and agreed upon societal values? A process to do this is described, and the final resolutions developed by the project (and included in a published report of the project "Society Must Decide") dealt with topics such as (1) autonomy and dignity, (2) prevention of disease, (3) access and justice, (4) cost control and (5) allocation for fairness. And, perhaps most important, the project has apparently resulted in some specific actions being taken by the state, concerned citizens and members of the medical profession itself.

And why might the Oregon Health Decisions project be of wider interest? It appears to link the allocation of health care resources to health care needs as these are perceived by community leaders who become knowledgeable about both. Then, through "town hall" discussions, they determine and agree upon community values and from these recommend allocation of societal resources for health care. (The process is called "biovaluation" in this article.) If such a process can be made

to work, it might be considerably more honest and more civilized than the unresponsible and often heartless de facto rationing of care that is now occurring, seemingly for lack of a better alternative.

MSMW

The Breadth of In Vitro Fertilization and Embryo Transfer

IN VITRO FERTILIZATION is clearly an idea whose time has come. It has thus far had profound ramifications on all aspects of reproductive medicine. It has influenced patient management and evaluation and shed new light on underlying pathophysiologic mechanisms that were previously a mystery. Consider the patient with unexplained infertility. As part of her workup and management, she may now have a cycle of hyperstimulation of oocytes based on the principle learned from in vitro fertilization that the more embryos placed in the uterus, the more likely a conception is to occur in any individual cycle. If all other treatment modalities fail, this patient may then go into an in vitro fertilization program which now presents a new treatment for her, with the potential of obviating the dead end met by previous procedures. This procedure has changed the face of the practice of reproductive endocrinology in a way that nothing else has.

The symposium "Extracorporeal Fertilization and Embryo Transfer in the Treatment of Infertility," appearing elsewhere in this issue, looks at but one aspect of this controversial area in that it compares and contrasts embryo transfer after in vivo fertilization versus embryo transfer after in vitro fertilization. Before embarking on a discussion as to the contrast between these two clinical processes, one is confronted with the great similarity seen. Eventually, fertilization and embryogenesis are the same in both procedures. It is only incubation and embryo transfer that differ in a technical way and the genetic makeup of the fetus that differs in a substantive way.

Critical to both processes is fertilization: once an oocyte is penetrated by a sperm, the second meiotic division occurs. Cortical granules are then activated which prevent penetration of further sperm into the ooplasm. This, as Zamboni describes, is the cortical reaction. Time is required after ovulation occurs for the oocyte to become ready to receive the spermatozoon. This usually occurs in the ampullary portion of the tube. This one biological condition provides both strict constraints on the timing of ovum capture for extracorporeal fertilization and also a window by which delayed exposure to sperm can be determined. After the oocytes are collected, they are inspected in the laboratory; if they are mature or intermediate based on cumulus dispersion, then exposure to spermatozoa within six hours is the rule. If they are immature, the eggs are allowed to incubate for 24 hours and are then exposed to spermatozoa. Trounson and co-workers in 1982 reported on the effectiveness of delayed insemination in an in vitro fertilization procedure.[1] This description allows for the less precise timing of ovum capture. By allowing immature eggs to mature in vitro for 24 hours, these, too, can be inseminated and result in embryos for transfer and eventual pregnancy. In some groups the number of immature eggs captured is as high as 20%.

Grading eggs as to maturity based on cumulus dispersion, simply stated, is that the more mature the egg, the more likely is the cumulus to be dispersed, thus facilitating sperm penetration. Studies have shown that in stimulated cycles, a discrepancy may occur between oocyte maturity as judged by cumulus dispersion and actual oocyte maturity based on ovum architecture.[2] Acrosomal enzymes help disperse the cumulus mass, thus aiding fertilization. Once the sperm head is in contact with the zona pellucida, the acrosome is released as protease, destroying the "last barrier separating (sperm) from the oocyte." The two pronuclei then undergo syngamy. Genetic material between the two gametes is mixed, followed by cleavage of the cell and eventual embryogenesis.

In the most successful centers around the world that provide in vitro fertilization and embryo transfer, the success rate, defined as a clinical pregnancy occurring after a laparoscopy to retrieve ovum, is approximately 20%. The viable pregnancy rate approaches 17%.[3] Therefore, the thrust in this procedure must be towards improving success rates per cycle. How can we best accomplish this, and where should this flurry of activity surrounding in vitro fertilization and embryo transfer be aimed? Basically, there are two important time frames to be investigated: one is the period of ovulation induction and the second is implantation. Little to nothing is known about the implantation of the human embryo, for obvious reasons. Given our current level of information, it would be hard to even construct sophisticated clinical studies to look at implantation of the human embryo. For this reason, scrutiny of ovulation induction as a reflection of normal embryogenesis takes on significance. In contrast, the laboratory environment for embryogenesis has not in the past few years been accorded the importance that it should.

Ovulation and ovulation induction are a complicated cascade of events, and attempts are being made to determine markers of successful ovulation induction. These attempts include monitoring peripheral estrogen levels, doing ultrasonography and studying follicular fluid contents. Through the use of cell culture, the performance by various cellular components of the follicle, including the granulosa cells and the cumulus corona complex, is being investigated. Peripheral blood measurements have shown that estrogen levels, which rise with the administration of human chorionic gonadotropin, correlate with increased success rates.[4] Cyclic adenosine monophosphate has been evaluated in follicular fluid and seems to correlate inversely with maturity of the oocyte and thus pregnancy rates.[5] Studies that involve the cumulus corona complex show that a high ratio of estradiol to testosterone correlates with higher fertilization and cleavage rates.[6]

Ovulation induction, therefore, remains the key, at least today, for successful in vitro fertilization. As best we can tell, proper induction of ovulation with a normal surrounding hormonal milieu best correlates with normal embryo development and pregnancy. What can be done to manipulate normal ovulation induction and make it successful, and what goals are we trying to achieve? The ideal would be four oocytes, all at the same level of maturity (preovulatory), surrounded by a system with a hormonal milieu conducive to implantation. The problem is that with most ovulation induction methods used, various cohorts of follicles are recruited as a function of time, making asynchrony a significant problem. Attempts have been made to change the treatment regimen in various ways but none have been satisfactory. A theoretical concept in humans to control ovulation more precisely would be to turn